

In the Claims

Please amend the claims presented during the international phase as follows.

Applicant presents a full set of claims showing markups of the claims with insertions and deletions indicated by underlining (or double bracketing) and strikethrough text, respectively.

1. (Original) An anti-TNF-alpha polypeptide comprising at least one anti-TNF-alpha single domain antibody.
2. (Original) An anti-TNF-alpha polypeptide according to claim 1 wherein a single domain antibody corresponds to a sequence represented by any of SEQ ID NOs: 1 to 16 and 79 to 84.
3. (Currently amended) An anti-TNF-alpha polypeptide according to claim 1 ~~claims 1 and 2~~ further comprising at least one single domain antibody directed against a serum protein.
4. (Currently amended) An anti-TNF-alpha polypeptide according to claim 3 ~~any of claims 1 to 3~~ wherein said serum protein is any of serum albumin, serum immunoglobulins, thyroxine-binding protein, transferrin ~~transferring~~, or fibrinogen.
5. (Currently amended) An anti-TNF-alpha polypeptide according to claim 3 ~~claims 3 and 4~~ wherein ~~a single domain~~ the anti-serum protein single domain antibody correspond to a sequence represented by any of SEQ ID NOs: 26 to 29 and 85 to 97.
6. (Currently amended) An anti-TNF-alpha polypeptide according to claim 3 ~~any of claims 3 to 5~~ corresponding to a sequence represented by any of SEQ ID NOs: 30 to 43.
7. (Currently amended) An anti-TNF-alpha polypeptide according to claim 1 ~~any of claims 1 to 6~~ further comprising at least one single domain antibody selected from the group consisting of anti-IFN-gamma single domain antibody, anti-TNF-alpha receptor single domain antibody and anti-IFN-gamma receptor single domain antibody.

8. (Currently amended) An anti-TNF-alpha polypeptide according to claim 1 ~~any of claims 1 and 7~~, wherein the number of single domain antibodies directed against TNF-alpha is at least two.
9. (Original) An anti-TNF-alpha polypeptide according to claim 8 corresponding to a sequence represented by any of SEQ ID NOs: 73 to 76.
10. (Currently amended) An anti-TNF-alpha polypeptide according claim 1 ~~any of claims 1 to 9~~, wherein at least one single domain antibody is a humanized *Camelidae* VHHs.
11. (Original) An anti-TNF-alpha polypeptide according to claim 10 wherein a humanized *Camelidae* VHH corresponds to a sequence represented by any of SEQ ID NOs: 17 to 19 and 21 to 24.
12. (Currently amended) A composition comprising an anti-TNF-alpha polypeptide according to claim 1 ~~any of claims 1 to 11~~ and at least one single domain antibody from the group consisting of anti-IFN-gamma single domain antibody, anti-TNF-alpha receptor single domain antibody and anti-IFN-gamma receptor single domain antibody, for simultaneous, separate or sequential administration to a subject.
13. (Currently amended) An anti-TNF-alpha polypeptide according to claim 7 ~~any of claims 7 to 11, or a composition according to claim 12~~ wherein the at least one anti-IFN-gamma single domain antibody ~~correspond~~ corresponds to a sequence represented by any of SEQ ID NOs: 44 to 72.
14. (Canceled)
15. (Currently amended) An anti-TNF-alpha polypeptide according to claim 1 ~~any of claims 1 to 11 and 13 and 14, or a composition according to claims 12 to 14~~, wherein the anti-TNF-alpha polypeptide is an homologous sequence, a functional portion, or a functional portion of an homologous sequence of the full length anti-TNF-alpha polypeptide.

16. (Currently amended) An anti-TNF-alpha polypeptide according to ~~any of claim 1 to 11, and 13 to 15, or a composition according to claims 12 to 15~~ wherein the at least one single domain antibody is a *Camelidae* VHH.

17. (Currently amended) A nucleic acid encoding an anti-TNF-alpha polypeptide according to claim 1 ~~any of claims 1 to 16~~.

18. (Currently amended) A method of identifying an agent that modulates the binding of an anti-TNF-alpha polypeptide ~~of any of claims 1 to 11, and 13 to 16~~, to Tumor Necrosis Factor-alpha comprising the steps of:

- (a) contacting an anti-TNF-alpha polypeptide of claim 1 ~~any of claims 1 to 11, and 13 to 16~~ with a target that is Tumor Necrosis Factor alpha, in the presence and absence of a candidate modulator under conditions permitting binding between said polypeptide and target, and
- (b) measuring the binding between the polypeptide and target of step (a), wherein a decrease in binding in the presence of said candidate modulator, relative to the binding in the absence of said candidate modulator, identifies ~~identified~~ said candidate modulator as an agent that modulates the binding of an anti-TNF-alpha polypeptide ~~of any of claims 1 to 11, and 13 to 16~~ and Tumor Necrosis Factor-alpha.

19. (Currently amended) A method of identifying an agent that modulates Tumor Necrosis Factor-alpha-mediated disorders through the binding of an anti-TNF-alpha polypeptide ~~of any of claims 1 to 11, and 13 to 16~~ to Tumor Necrosis Factor-alpha comprising:

- (a) contacting an anti-TNF-alpha polypeptide of claim 1 ~~any of claims 1 to 11, and 13 to 16~~ with a target that is Tumor Necrosis Factor alpha, in the presence and absence of a candidate modulator under conditions permitting binding between said polypeptide and target, and
- (b) measuring the binding between the polypeptide and target of step (a), wherein a decrease in binding in the presence of said candidate modulator, relative to the binding in the absence of said candidate modulator, identifies ~~identified~~, said candidate modulator as an agent that modulates Tumor Necrosis Factor alpha-mediated disorders.

20. (Currently amended) A method of identifying an agent that modulates the binding of Tumor Necrosis Factor alpha to its receptor through the binding of an anti-TNF-alpha polypeptide of ~~any of claims 1 to 11, and 13 to 16~~ to Tumor Necrosis Factor-alpha comprising:

(a) contacting an anti-TNF-alpha polypeptide of claim 1 ~~any of claims 1 to 11, and 13 to 16~~ with a target that is Tumor Necrosis Factor-alpha, in the presence and absence of a candidate modulator under conditions permitting binding between said polypeptide and target, and

(b) measuring the binding between the polypeptide and target of step (a), wherein a decrease in binding in the presence of said candidate modulator, relative to the binding in the absence of said candidate modulator, identifies ~~identified~~ said candidate modulator as an agent that modulates the binding of Tumor Necrosis Factor-alpha to its receptor.

21. (Currently amended) A kit for screening for agents that modulate Tumor Necrosis Factor-alpha-mediated disorders comprising an anti-TNF-alpha polypeptide of claim 1 ~~any of claims 1 to 11, and 13 to 16~~ and Tumor Necrosis Factor-alpha.

22.-25. (Canceled)

26. (Currently amended) A method for treating and/or preventing and/or alleviating disorders relating to inflammatory reactions comprising administering to a subject in need of such treatment an effective amount of the Use of an anti-TNF-alpha polypeptide of claim 1 ~~any of claims 1 to 11, and 13 to 16 or a nucleic acid according to claim 17, or a composition according to any of claims 12 to 16, or an agent according to any of claims 20 to 21 for the preparation of a medicament for treating and/or preventing and/or alleviating disorders relating to inflammatory reactions.~~

27. (Canceled)

28. (Currently amended) A method for treating and/or preventing and/or alleviating the symptoms of disorders susceptible to modulation by a TNF-alpha modulating substance, comprising administering to a subject in need of such treatment Use of an anti-TNF-alpha polypeptide of claim 1 ~~any of claims 1 to 11, and 13 to 16 or a composition according to any~~

~~of claims 12 to 16, for the preparation of a medicament for treating, preventing and/or alleviating the symptoms of disorders susceptible to modulation by a TNF-alpha modulating substance which is able pass that passes through the gastric environment without the substance being inactivated.~~

29. (Canceled)

30. (Currently amended) A method for treating and/or preventing and/or alleviating disorders susceptible to modulation by a TNF-alpha modulating substance delivered to the vaginal and/or rectal tract, or the nose, upper respiratory tract and/or lung, comprising administering to the vaginal and/or rectal tract, or the nose, upper respiratory tract and/or lung, of a subject in need of such treatment an effective amount of Use of an anti-TNF-alpha polypeptide of claim 1 any of claims 1 to 11, and 13 to 16 or a composition according to any of claims 12 to 16, for the preparation of a medicament for treating, preventing and/or alleviating the symptoms of disorders susceptible to modulation by a TNF-alpha modulating substance delivered to the vaginal and/or rectal tract.

31.-33. (Canceled)

34. (Currently amended) A method for treating and/or preventing and/or alleviating the symptoms of disorders susceptible to modulation by a TNF-alpha modulating substance delivered to the intestinal mucosa, wherein said disorder increases the permeability of the intestinal mucosa, comprising administering to the intestinal mucosa of a subject in need of such treatment Use of an anti-TNF-alpha polypeptide of claim 1 any of claims 1 to 11, and 13 to 16 or a composition according to any of claims 12 to 16, for the preparation of a medicament for treating, preventing and/or alleviating the symptoms of disorders susceptible to modulation by a TNF-alpha modulating substance delivered to the intestinal mucosa, wherein said disorder increases the permeability of the intestinal mucosa.

35. (Canceled)

36. (Currently amended) A method for treating and/or preventing and/or alleviating the symptoms of disorders susceptible to modulation by a TNF-alpha modulating substance, comprising administering to a subject in need of such treatment Use of an anti-TNF-alpha

polypeptide of claim 1 ~~any of claims 1 to 11, and 13 to 16 or a composition according to any of claims 12 to 16, for the preparation of a medicament for treating, preventing and/or alleviating the symptoms of disorders susceptible to modulation by a TNF-alpha modulating substance which is able pass~~ that passes through the tissues beneath the tongue effectively.

37. (Canceled)

38. (Currently amended) A method for treating and/or preventing and/or alleviating the symptoms of disorders susceptible to modulation by a TNF-alpha modulating substance, comprising administering to a subject in need of such treatment Use of an anti-TNF-alpha polypeptide of claim 1 ~~any of claims 1 to 11, and 13 to 16 or a composition according to any of claims 12 to 16, for the preparation of a medicament for treating, preventing and/or alleviating the symptoms of disorders susceptible to modulation by a TNF-alpha modulating substance which is able pass~~ that passes through the skin effectively.

39. (Currently amended) A method according to ~~claim 19, a kit according to claim 21, a nucleic acid or agent according to claim 25, use of a nucleic acid or agent according to claim 26, a composition according to any of claims 25, 27, 29, 31, 33, 35, 37 and 39, use of a composition according to any of claims 26, 28, 30, 32, 34, 36, and 38, an anti-TNF-alpha polypeptide of any of claims 25, 27, 29, 31, 33, 35, 37 and 39, use of an anti-TNF-alpha polypeptide according to any of claims 26, 28, 30, 32, 34, 36, and 38~~ wherein said disorders are any of inflammation, rheumatoid arthritis, Crohn's disease, ulcerative colitis, inflammatory bowel syndrome, multiple sclerosis, Addison's disease, Autoimmune hepatitis, Autoimmune parotitis, Diabetes Type I, Epididymitis, Glomerulonephritis, Graves' disease, Guillain-Barre syndrome, Hashimoto's disease, Hemolytic anemia, Systemic lupus erythematosus, Male infertility, Multiple sclerosis, Myasthenia Gravis, Pemphigus, Psoriasis, Rheumatic fever, Rheumatoid arthritis, Sarcoidosis, Scleroderma, Sjogren's syndrome, Spondyloarthropathies, Thyroiditis, and Vasculitis.

40. (Currently amended) A composition comprising ~~a nucleic acid or agent according to claim 25, an~~ the anti-TNF-alpha polypeptide of claim 1 ~~any of claims 1 to 11 and 13 to 16, or a composition according to any of claims 12 to 16,~~ and a suitable pharmaceutical vehicle.

41. (Currently amended) A method of diagnosing a disorder characterised by the dysfunction of Tumor Necrosis Factor-alpha comprising:

- (a) contacting a sample with an anti-TNF-alpha polypeptide of claim 1 ~~any of claims 1 to 11, and 13 to 16,~~
- (b) detecting binding of said polypeptide to said sample, and
- (c) comparing the binding detected in step (b) with a standard, wherein a difference in binding relative to said sample is diagnostic of a disorder characterised by dysfunction of Tumor Necrosis Factor-alpha.

42.-43. (Canceled)

44. (Currently amended) A method for purification of Tumor Necrosis Factor-alpha, comprising contacting a sample with the Use of an anti-TNF-alpha polypeptide of claim 1 ~~any of claims 1 to 11, and 13 to 16 for the purification of said Tumor Necrosis Factor-alpha.~~

45. (Currently amended) A method Use of an anti-TNF-alpha polypeptide of any of claims 1 to 11, and 13 to 16 for inhibiting the interaction between Tumor Necrosis Factor-alpha and one or more Tumor Necrosis Factor-alpha receptors, comprising contacting Tumor Necrosis Factor-alpha with the anti-TNF-alpha polypeptide of claim 1.

46. (Currently amended) A method for producing an anti-TNF-alpha polypeptide of claim 1 ~~any of claims 1 to 11, and 13 to 16~~ comprising the steps of:

- (a) obtaining double stranded DNA encoding a *Camelidae* VHH directed to Tumor Necrosis Factor alpha,
- (b) cloning and expressing the DNA selected in step (b).

47. (Currently amended) A method of producing an anti-TNF-alpha polypeptide of claim 1 ~~any of claims 1 to 11, and 13 to 16~~ comprising:

- (a) culturing host cells comprising nucleic acid ~~eapable of encoding~~ that encode an anti-TNF-alpha polypeptide of claim 1 ~~any of claims 1 to 11, and 13 to 16,~~ under conditions allowing the expression of the polypeptide, and,
- (b) recovering the produced polypeptide from the culture.

48. (Original) A method according to claim 47, wherein said host cells are bacterial or yeast.

49. (Canceled) ~~A kit for screening for any of inflammation, rheumatoid arthritis, Crohn's disease, ulcerative colitis, inflammatory bowel syndrome or multiple sclerosis comprising an anti-TNF-alpha polypeptide of any of claims 1 to 11, and 13 to 16.~~